REMARKS

I. Status of the claims

Claim 70 has been amended and claim 129 has been canceled. Thus, claims 70-72, 74-77, 79-98 and 129-163 are pending in the case and claims 99-129 stand withdrawn.

II. Information disclosure statements

This paper is submitted along with a supplementary information disclosure statement. The Examiner is requested to review the attached a statement and is also requested to review the statement dated March 21, 2007, that does not appear to have been considered previously.

III. The rejection under 35 U.S.C. § 103 should be withdrawn

In a Final Office Action dated March 16, 2007 the Examiner rejected all claims as obvious under 35 U.S.C. § 103, over Shabram (U.S. Patent 5,837,520), Huyghe *et al.* (Human Gene Therapy, 1995), Kozak *et al.* (Developments in Biological Standardization, 1996), Keay *et al.* (Biotechnology and Bioengineering, 1976), Nadeau *et al.* (Biotechnology and Bioengineering) and Griffiths (Animal Cell Biotechnology, 1986). However, many of the cited references are not relevant to the rejection made with respect to the main independent claim 70, from which all the remaining claims depend. According to the Examiner's analysis Huyghe concerns methods for adenoviral purification involving various steps including cesium chloride purification and column chromatography wherein viral particle to PFU ratio is determined (March 16, 2007 Action at pages 5 and 6). However, claim 70 does not recite limitations concerning any of these elements. Likewise, Kozak concerns monitoring of bovine protein contamination in products as it related to prevention of prion mediated disease and Keay concerns serum free culture conditions for the replication of certain viruses. However, neither Kozak nor Keay seem to be applicable to the rejection as it related to amended claim 70 because no purity limitation concerning protein contamination or serum free culture is recited in the claim. Finally, Griffiths is alleged to teach the importance of microcarriers in the scale-up of cell populations but is not believed relevant to the rejection

of claim 70. In view of the foregoing, Applicants rebuttal of the instant rejection is limited to claim 70 as rejected over Shabram in view of Nadeau.

A. References cited by the examiner fail to teach all elements of the claims

The references cited in the instant rejection under 35 U.S.C. § 103 fail to teach all elements of the claims and thus no *prima facie* case has been made. In particular, the Examiner has failed to identify any reference that teaches the claimed level of the purity for an adenovirus composition as recited in claim 70 (*i.e.,* a contaminating nucleic acid content of less than 400 pg per 10^{10} pfu virus and greater than or equal to about 60 pg per 10^{10} pfu virus).

The primary reference cited by the Examiner, Shabram, never compares or even suggests comparing the amount of contaminating nucleic acid to the amount virus in a sample as assessed by PFU or any other measure. In an attempt to address this short-fall the Examiner states that Shabram teaches "the use of Benzonase, a highly efficient nuclease, could reduce or eliminate the presence of such nucleic acids from their Adenovirus preparation," (March 16, 2007 Action at page 4). Thus, the Examiner appears to suggest that the low level of contaminating nucleic acid recited in the claims is inherent in the teachings of Shabram. Applicants disagree and note that the Patent Office has previously analyzed Shabram with respect to the level of nucleic acids contamination adenoviral preparations and found that it DOES NOT teach the claimed low level of contamination. The Examiner is invited to review Applicants previous patent U.S. 6,726,907.

In the instant case, the Examiner has failed to provide sufficient evidence that Shabram teaches adenoviral compositions that achieve the requisite level of purity and therefore has failed to demonstrate that Shabram inherently teaches this element of the claims. The Federal Circuit has held that a proper rejection their must be supported by "substantial evidence" within the record, the Examiner has failed to meet this burden. *In re Gartside,* 203 F.3d 1305, 1315 (Fed. Cir. 2000). In the case where a rejection relies upon the doctrine of inherency, inherency *may not* be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *In re Roberstson*, 169 F.3d 743, 745 (Fed. Cir 1999); *Continental Can Co. v. Monsanto Co.,*

948 F.2d 1264, 1269 (Fed. Cir. 1994). Furthermore any extrinsic evidence that is relied upon must "make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *Telemac Cellular Corp. v. Topp Telecom, Inc.* 247 F3d 1316, 1328 (Fed. Cir. 2001); *In re Roberstson,* 169 F.3d 743, 745 (Fed. Cir 1999); *Continental Can Co. v. Monsanto Co.,* 948 F.2d 1264, 1269 (Fed. Cir. 1994). It is clear that the current rejection has not met this burden.

The Examiner attempts to demonstrate the alleged inherent teachings of Shabram by citation of Sastry *et al.* (Human Gene Therapy, 2004) and a description of a commercially available benzonase enzyme (Novagen® & Calbiochem®, Sample Preparation Tools for protein Research, 2nd Edition, 2006). However, neither of these references constitutes substantial evidence in support of the rejection. The cited product description is dated from 2006 and thus provides no information regarding benzonase enzyme preparations that were available to Shabram a decade earlier. Furthermore, the product description provides no teaching regarding the effectiveness of benzonase to reduce contaminating nucleic acid levels in an adenoviral composition nor does it provide any information regarding the amount of contaminating nucleic acid reduction that can be achieved by benzonase treatment.

Likewise, the Sastry reference does not provide teaching that is relevant to the instant rejection. The Examiner is referred to the declaration by Dr. Zhang regarding its discussion of the Sastry as it relates to the teachings of Shabram. In particular, Sastry teaches the use of benzonase treatment in *purified* lentiviral preparations. Sastry indicated that several treated preparations had an undetectable level of contaminating nucleic acid following treatment yet the treated lentivirus preparations are completely different from the crude adenovirus preparations of Shabram. First of all, the virus preparations of Sastry are cell culture supernatants and not cell lysates. As described by Dr. Zhang, cell culture supernatants do not comprise the high levels of contaminating cellular nucleic acids and other intracellular components that cell lysates contain. Thus, the preparations of Sastry have lower initial nucleic acid contamination and lower overall contamination as compared to the Shabram cell lysates. By virtue of its lower overall contamination, a cell supernatant preparation such as those in Sastry can be digested much more efficiently by enzymes such as benzonase. Furthermore, the preparations that are treated with benzonase by Sastry were

further purified by either ultracentrifugation or ultrafiltration PRIOR to benzonase treatment. Again these additional steps would be expected by the skilled artisan to reduce nucleic acid contamination and overall contamination thereby enabling a later benzonase treatment to be more effective in reducing the amount of contaminating nucleic acid. On the other hand, Shabram teaches only treatment of crude cell lysate with benzonase, followed by further column purification. As stated by Dr. Zhang, benzonase has reduced activity when used in a crude cell lysate as compared to in purified preparations such as those described in Sastry. For example, Dr Zhang indicates that the pH of a sample can significantly effect enzymatic activity. Thus, the skilled artisan would not expect the compositions of Shabram to achieve a nucleic acid contamination purity level relative to nucleic acid contamination that approaches the level of purity recited in claim 70. The references cited by the Examiner fail to demonstrate that the claimed level of purity would necessarily result from the methods of Shabram and thus the Examiner has failed to support the rejection with the requisite "substantial evidence."

B. References cited in the rejection can not be properly combine for a rejection under 35 U.S.C. § 103

The rejection set forth by the Examiner has cited, Nadeau with regard to teaching of batch-fed cell culture. As previously argued by Applicants, Nadeau does not concern adenovirus production, but rather protein production albeit from an adenoviral vector. For this reason Nadeau is not properly combined with other references that concern adenoviral purification such as Shabram in order to make a *prima facie* obviousness rejection of the claims. In support of this point, Applicants summit herewith a declaration from Dr. Peter Clarke that provides a detailed analysis of the Nadeau reference.

1. There would be no motivation to combine the cited references

As described by Dr. Clarke, the skilled worker would recognize that the teachings of Nadeau concern cell culture methods that increase protein yield from mammalian cells. Thus, these methods would be applicable to optimizing cell culture systems for *production of protein*, but would not be recognized as applicable to methods for adenovirus production. Thus, the skilled artisan would not be motivated to combine the

teachings of Nadeau with, for example, the teachings of Shabram since the two references concern production of completely different compositions (*i.e.*, proteins versus virus particles).

Dr. Clarke details the differences between virus production and protein production to highlight why the skilled artisan would recognize that the two process a requiring different cell culture parameters. First, Nadeau studies only protein production in mammalian cells. The studied proteins are expressed from an adenoviral vector, however virus production is not studied and virus yield is never addressed in Nadeau. Furthermore, the promoter used by Nadeau for protein expression is an adenoviral promoter that has been modified to increase its activity. Thus, the protein production observed in Nadeau is not indicative of viral protein production much less viral particle production. Nadeau also indicates that protein producing cells in the study display a high level of metabolic activity. However, as Dr. Clarke observes, high metabolic activity is counter indicative of high level virus production because viral replication, in particular adenoviral replication, mediates cellular metabolic shut down (see, *e.g.*, Zhang & Schneider 1994). For this reason a skilled artisan would recognize that adenoviral particle production in the studies of Nadeau is likely to be quite low.

Finally, Dr. Clarke discusses a reference by Cote *et al.* that clearly demonstrates that protein production from adenoviral vectors does not correlate with adenovirus particle production. Thus, upon review of Nadeau a skilled worker would find that the subject cell culture techniques are optimized for protein production and that protein production does not correlate with (and may counter indicative of) viral particle production. These findings would lead to a lack of motivation to combine the teaching of Nadeau with those of, for example Shabram, in order to "scale-up" adenoviral production. Nadeau provides no teaching to indicate that cell culture techniques can lead to enhanced purity level in protein preparations, much less high purity adenovirus preparations.

2. There would be no expectation of success in combining the cited references

The foregoing arguments not withstanding, there would be no reasonable expectation success in the combination of cell culture techniques of Nadeau with references

such as Shabram. As described above Nadeau concerns cell culture methods to enhance protein production in cells and at best provides no teaching regarding cell culture conditions that would be favorable for virus production. Thus, the skilled worker seeking improved methods for purifying adenovirus would not reasonably expect to be successful in using cell culture techniques of Nadeau to achieve an improved method for production (much less purification) of adenovirus. Nadeau does not provide any teaching regarding virus production and in some cases presented results such as metabolic data from producer cells suggest that the described culture techniques may stifle virus production. Thus, a skilled artisan would have no reason to believe that methods of Nadeau could be applied to achieve enhanced methods for adenoviral *purification*.

3. Nadeau teaches away from the claimed invention

Even if the skilled artisan was to equate protein yield in cells with virus yield (and as described by Dr. Clarke they would not) Nadeau teaches away from the claimed invention. In particular, as detailed by Dr. Clarke, Nadeau shows that the use of fed-batch culture techniques *prior to* infection resulted in the lowest specific protein production rate (see, *e.g.*, Table I of Nadeau)! Thus, even if a skilled worker assumed that a level of protein production would correspond to viral particle production, Nadeau would teach away from the use of batch-fed culture prior to infection.

IV. Conclusion

In view of the above amendment and argument, Applicants believes the pending application is in condition for allowance and such favorable action is requested. The Examiner is invited to contact the undersigned to discuss the case.

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Respectfully submitted,

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